NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

STRATEGIC PLAN

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NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

STRATEGIC PLAN

Executive Summary

Introduction

Much progress has been made in reducing the burden of diseases of the heart, blood vessels, lungs, and blood. And yet, heart disease remains the leading cause of death in the United States with deaths from congestive heart failure on a steadily upward course; death rates for asthma continue to increase; the incidence and prevalence of chronic obstructive pulmonary disease (COPD) has risen, making it the fourth most common cause of death in the United States; and there is still no completely satisfactory way of treating sickle cell disease and other blood disorders. It is clear that much remains to be done. It is also clear that the current paths of research offer promise for profoundly improved methods of preventing, diagnosing, and treating the diseases and disorders that constitute the mandate of the National Heart, Lung, and Blood Institute (NHLBI).

Purpose of the NHLBI Strategic Plan

The legislative mandate to the NHLBI is to provide leadership for a national program in diseases of the heart, blood vessels, lungs, and blood; sleep disorders; and blood resources. This strategic plan presents, for the years FY 2001-2005, important scientific opportunities within the Institute's mandate, as well as selected action steps that can be taken to address them. The plan is intended primarily to inform the public about those opportunities so that they can become more effectively involved in helping the Institute to set priorities among them.

It is important to recognize that the plan cannot and is not intended to reflect the full range of NHLBI-supported research. Presently the NHLBI research portfolio encompasses all disease areas within the Institute's mandate and includes research ranging from basic studies in cellular and molecular biology and physiology to clinical trials and epidemiological studies. This plan is directed only to the part of the Institute portfolio that we refer to as Institute-initiated research (i.e., research solicited by the NHLBI to address specific Institute-identified subject areas). It does not include the large investigator-initiated component (i.e., those research projects that are proposed by investigators to address subject areas that they, themselves, identify) that comprises approximately three-quarters of the research supported by the Institute. Moreover, the plan is focused on future research investments. It is not intended to present a comprehensive view of all of the research areas currently receiving NHLBI support.

As with any plan for the future, we expect it to be flexible and dynamic so that the Institute will be able to respond to evolving national needs, Congressional mandates, and advances in scientific knowledge. The opportunities and selected action steps identified in the plan were derived from numerous and extensive discussions and thorough reviews by representatives of the scientific community and by Institute advisory committees and working groups.

Formulation of the Plan

Formulation of the plan began in May 1998 when the Institute assembled a select group of accomplished scientists to assist it by identifying those research areas that constitute extraordinary opportunities and merit substantial increases in resource investment.

The Institute then convened a September 1998 conference to allow the select group of scientists and Institute staff to meet with representatives invited by three of the major professional societies associated with the mission of the NHLBI, i.e., the American Heart Association, the American Thoracic Society, and the American Society of Hematology. Our objective in bringing the groups together was not to elicit their ideas on research directions that address the separate interests of their individual societies but, rather, to ask them to focus on broad research themes that transcend the traditional organ-specific domains within the Institute. The report of the Conference has been widely disseminated, it has been posted on the Institute's web site (http://www.nhlbi.nih.gov/funding/fromdir/sparkweb.htm), and it has provided the underlying basis for this plan. Institute staff, working with the guidance of the Conference report, then formulated goals and action steps to be addressed over the next several years.

In addition, the Institute's newly formed Board of Extramural Advisors (BEA) and the National Heart, Lung, and Blood Advisory Council (NHLBAC) have studied the plan and provided guidance and suggestions. The BEA is a working group of the Council, consisting of scientists of significant stature in the cardiovascular, lung, blood, and sleep research communities, that is charged with evaluating the NHLBI research and training portfolios on an ongoing basis. Its assessments of proposed research initiatives have been incorporated into this plan.

After review and revision of the plan to reflect the views of the BEA and the NHLBAC, the document was distributed to the major professional organizations related to the mission of the NHLBI and posted on the Institute's web site for public review. Comments and suggestions were solicited from both the organizations and the public, and appropriate revisions have been made.

Organization of the Plan

The plan is organized around seven major areas that reflect the broad mandate of the Institute:

- Development and Progression of Disease
- Diagnosis of Disease
- Treatment of Disease
- Maintenance of Health Through Prevention of Disease
- Translation of Research Results Into Practice
- Reduction of Health Disparities
- Research Workforce and Research Resources.

Several specific scientific opportunities (i.e., Goals) have been identified within each of the areas. Each of them is considered to be important; no significance is intended by their order of presentation. Several of the goals are interrelated in that research results from one area will often provide important information for related research in another area. Potential FY 2001 initiatives currently being developed and reviewed, as ways to stimulate interest in the identified

scientific opportunities, can be found under their corresponding goals in the full strategic plan. These are the priority steps under consideration for FY 2001. Additional actions to be undertaken in the future that would contribute to realization of the research goals are also included in the full plan.

Strategic Plan Areas

- **Development and Progression of Disease**

An increased understanding of the processes and factors that underlie development and progression of disease is often a necessary first step toward devising new approaches to prevent and treat disease.

Goals are to identify the genetic variations that predispose individuals to development of cardiovascular, lung, and blood diseases and determine how they interact with environmental factors to cause disease; identify additional environmental factors that predispose individuals to development of these diseases; further understanding of the transitional events in disease progression; and relate cellular development and differentiation to establishment of disease.

- **Diagnosis of Disease**

Improved methods of disease diagnosis that are minimally invasive and permit earlier identification of disease are needed to enable more effective interventions to prevent or minimize the adverse effects of disease.

Goals are to develop and validate new methods of detecting inflammation-associated cardiovascular, lung, and blood diseases; apply genetic and genomic technologies to the diagnosis of these diseases; and identify and assess new risk factors for these diseases so that disease susceptibility can be predicted more reliably.

- **Treatment of Disease**

Improved methods of treatment are needed to ensure continued progress towards reducing the disability and mortality burden imposed by cardiovascular, lung, and blood diseases.

Goals are to develop a program in basic and clinical studies in gene therapy; identify the genetic basis for individual therapeutic and adverse responses to drugs used in cardiovascular, lung, and blood diseases; improve the outcome of heart and lung transplantation and increase the supply of donor organs; improve hematopoietic stem cell transplantation; develop the scientific underpinning necessary to be able to repair or replace damaged tissues and organs; and obtain information that would lead to evidence-based treatment decisions for patients with rare cardiovascular, lung, and blood diseases.

- **Maintenance of Health through Prevention of Disease**

Successful disease prevention efforts are invariably preferable to interventions to ameliorate or mitigate the adverse effects of established disease.

Goals are to improve understanding of how behavior affects the development of risk factors and determine how to combine lifestyle changes and medical management to prevent or reduce them; continue to improve blood transfusion safety; and develop more comprehensive dietary recommendations to improve cardiovascular health.

- **Translation of Research Results into Practice**

In order for research to have practical value for improving diagnosis, treatment, and prevention of disease, basic research findings must be tested in clinical studies, and recommendations for preventive and therapeutic interventions must be adopted by physicians and the public.

Goals are to examine factors that influence, and methods to increase, the dissemination and implementation of preventive interventions and evidence-based clinical treatment guidelines in medical practice; and facilitate the translation of basic research ideas to clinical investigation by, for example, developing innovative ways to provide resources required for clinical studies.

- **Reduction of Health Disparities**

Individuals who are of lower socioeconomic status (SES) or of minority status have worse health than higher SES and nonminority individuals. They experience higher rates of disability and death from cardiovascular disease, asthma, and sleep disorders. Some diseases develop differently in women than in men.

Goals are to improve health behaviors and outcomes in individuals of lower SES and in minority individuals, as well as to improve health-care seeking and delivery in these populations; improve understanding about mechanisms that cause diseases to develop and manifest themselves differently in women and men; improve the efficacy of diagnostic testing and treatment approaches in specific population groups; and improve understanding of how factors early in life contribute to health disparities later in life.

- **Research Workforce and Research Resources**

Workforce and resource requirements to support the research proposed in this strategic plan necessitate innovative approaches using state-of-the-art scientific technology and communication and information tools.

Goals are to use existing study populations more effectively and identify potential new study populations; increase the use of imaging techniques and improve access to imaging facilities; attract individuals into biomedical science (especially, clinical investigation); develop the potential uses of nanoscale materials (materials vanishingly small) and nanoscale technology in the design of diagnostic and therapeutic systems; and develop information resources and the capability to use them to enhance research efforts in cardiovascular, lung, and blood diseases and sleep disorders.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

STRATEGIC PLAN

Introduction

Diseases of the heart, blood vessels, lungs, and blood together accounted for 51 percent of all deaths in the United States in 1997. Their associated economic costs are estimated to represent 25 percent of the total economic costs due to illness, injury, and death in 1999. Heart disease is the leading cause of death in the United States, and with cerebrovascular disease ranking third and chronic obstructive pulmonary disease (COPD) ranking fourth, diseases within the legislative mandate for the National Heart, Lung, and Blood Institute (NHLBI) comprise three of our four leading causes of death.

Progress

In 1948, when the National Heart Institute—the forerunner of today's NHLBI—was founded, a heart attack signaled the end of an active life. One-third of the patients who reached a hospital died within weeks, and those who survived still faced a long ordeal. The only available treatments were painkillers and complete bed rest—6 weeks or more in the hospital and 6 months before patients could sit up in a chair. Since then advances such as intensive and coronary care units, surgical techniques to repair heart damage, and drugs and preventive measures to control the conditions that lead to a heart attack have dramatically changed all that. Today most patients return to normal activities within weeks of a heart attack. And in the past 30 years, the national age-adjusted death rate for coronary heart disease has decreased by more than half.

Dramatic changes have also occurred in the management and treatment of other diseases within the Institute's mandate. In the 1940s, sports were off-limits for most children with asthma. Although bronchodilator drugs were developed in the 1950s to combat asthma attacks, the cause of attacks remained unknown until research in the 1970s and 1980s led to a new way of looking at asthma. As a result, asthma was recognized as a chronic inflammatory lung disease that could be monitored and treated with daily medication to prevent acute attacks. Now, people with asthma lead long and active lives, participate in sports, and even compete in the Olympics.

And then there is sickle cell disease. Until the early 1970s, treatment for sickle cell disease consisted primarily of blood transfusions and management of recurrent attacks of pain; many patients did not survive past young adulthood. Yet, within 25 years, the average life expectancy for sickle cell patients had more than doubled. A new drug treatment is now available that reduces the number of painful crises by half, thereby greatly improving patients' lives.

These advances and many others reflect the great progress that has been made in reducing the burden of cardiovascular, lung, and blood diseases. And yet, heart disease remains the

leading cause of death in the United States with deaths from congestive heart failure on a steadily upward course; death rates for asthma continue to increase; the incidence and prevalence of chronic obstructive pulmonary disease (COPD) (e.g., chronic bronchitis and emphysema) has risen, making COPD, including asthma, the fourth most common cause of death in the United States[1]; and there is still no completely satisfactory way of treating sickle cell disease and other blood disorders. It is clear that much remains to be done. It is also clear that the current paths of research offer promise for profoundly improved methods of preventing, diagnosing, and treating the diseases and disorders that constitute the mandate of the NHLBI.

Promise

Let us illustrate the future we envision with examples from the area of cardiovascular diseases.

Prevention — We all know that we are better off trying to prevent a disease than waiting for it to occur and then attempting to ameliorate or cure it once it is established. We also know that it is not realistic to expect complete success in preventing all cardiovascular, lung, and blood diseases within the foreseeable future. However, as new genetic information continues to accumulate, it is likely that more targeted and more effective approaches to disease prevention will rapidly become a reality. In the not-too-distant future, physicians may be using genetic markers to identify persons who are predisposed to develop cardiovascular diseases long before they show any clinical signs of disease. Physicians may also be able to predict with high reliability the most probable course of disease progression for their patients and then use that information to design the most effective intervention strategy for them.

Consider hypertension, one of the most prevalent chronic conditions in the United States, affecting an estimated 50 million people. We currently advocate general lifestyle and dietary practices that can prevent or at least substantially delay the onset of hypertension, but it is often difficult to motivate people to adopt healthy behaviors based solely on a general probability of developing disease, especially when the disease and its consequences may only manifest themselves many years in the future. On the other hand, if patients could be told that their individual genetic profile places them at particularly high risk for hypertension, it might be far easier to convince them of the need to modify their behavior.

Better treatment decisions are also likely for those who do become hypertensive. Genes have already been identified in hypertensive animals that are associated with development of kidney failure and stroke. As we improve our understanding of the mechanisms of action of the various antihypertensive agents, physicians may be able to match that knowledge with the genetic profile of their patients to customize their therapy, perhaps prescribing one class of drugs for those who are predisposed to strokes, another for those who are predisposed to kidney failure, another for those who are predisposed to heart failure, and yet another for those who are predisposed to heart attacks.

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[1]Other conditions related to the mission of the NHLBI ranked in the top ten causes of death in the United States are cerebrovascular disease (ranked 3rd) and respiratory infections (ranked 6th). Responsibility for lung cancer, which is a major component of cancer mortality (the second leading cause of death) lies with the National Cancer Institute.

Diagnosis — And what about those people who, because of their blood pressure, their cholesterol level, or their level of some other as-yet-unidentified risk factor, go on to develop coronary artery disease? For many of them, the current diagnostic standard, the angiogram, will almost certainly be a thing of the past. Noninvasive imaging techniques are already rapidly approaching the point where they can provide pictures of the coronary arteries at levels of resolution comparable to those of angiograms. Soon there will be no need to expose patients to the risk entailed in running a catheter through their arteries or the ionizing radiation associated with an angiogram, not to mention the discomfort associated with the procedure or the inconvenience of remaining motionless for an extended period of time after it is completed. There should also be no need to subject patients to additional tests to determine how effectively the heart is pumping or how well the blood it pumps is reaching the muscles of the heart itself. Magnetic resonance angiography is already as good as the established alternatives in providing that information.

Treatment — Perhaps even more impressive is how the treatment options for patients with coronary artery disease are likely to improve. Although some cases can be managed and even reversed by intensive interventions to modify risk factors, most serious cases require a form of physical intervention—either an angioplasty procedure in which the built-up areas within the coronary arteries are compressed against the artery wall or a coronary bypass procedure in which lengths of veins taken from another part of the body are sewn around the blockage. Both of these approaches have been highly successful and yet both entail significant drawbacks. Angioplasty is the far less invasive alternative, but angioplasties often fail, providing only short-term relief and necessitating a subsequent procedure, either another angioplasty or a bypass. In addition, problems occasionally arise during an angioplasty that can be resolved only by an emergency bypass.

As for bypass surgery, it may be routine—it is one of the most common surgical procedures performed in the United States—but it is major surgery nonetheless. In its most common form, it entails sawing the breastbone, separating the rib cage, and stopping the heart while circulation to the brain and other vital organs is maintained with an external heart–lung machine. In contrast, future “bypasses” may be naturally grown, the result of inserting normal human growth factors or the genes that produce them directly at the site of a blockage, perhaps through the use of a catheter threaded to the site or alternatively through a minimal incision between the ribs. In either case, the result would be a marked decrease in trauma to the patient.

Breadth of the Promise

The future of disease prevention, diagnosis, and treatment is equally promising for all of the other areas within the Institute’s mandate. Ongoing efforts to understand the genes involved in disease processes and their function in health and disease will not only point to possible targets for interventions to prevent or treat disease, but may even provide the therapeutic agents that can offset or compensate for defective human proteins, such as those causing cystic fibrosis or hemophilia. Expanded efforts to grow normal human tissues may enable physicians to repair or replace lung tissue ravaged by emphysema or heart tissue damaged by a heart attack. Further studies of the roles of inflammation and infection in disease processes can be expected to lead to better agents to prevent acute asthmatic attacks, and perhaps asthma itself.

This is not to say that all or even a substantial part of this promise is yet within reach. Much research remains to be done to bring us even close to that point. And yet, it is clear from the scientific opportunities now open to us that realization of all of it is just a matter of time. The purpose of this plan is to outline the logical next steps that we need to take toward making the promise of today the reality of the future.

Purpose of the NHLBI Strategic Plan

The legislative mandate to the NHLBI is to provide leadership for a national program in diseases of the heart, blood vessels, lungs, and blood; sleep disorders; and blood resources. This strategic plan presents, for the years FY 2001-2005, important scientific opportunities within the Institute's mandate, as well as selected action steps that can be taken to address them. The plan is intended primarily to inform the public about those opportunities so that they can become more effectively involved in helping the Institute to set priorities among them.

It is important to recognize that the plan cannot and is not intended to reflect the full range of NHLBI-supported research. Presently the NHLBI research portfolio encompasses all disease areas within the Institute's mandate and includes research ranging from basic studies in cellular and molecular biology and physiology to clinical trials and epidemiological studies. This plan is directed only to the part of the Institute portfolio that we refer to as Institute-initiated research (i.e., research solicited by the NHLBI to address specific Institute-identified subject areas). It does not include the large investigator-initiated component (i.e., those research projects that are proposed by investigators to address subject areas that they, themselves, identify) that comprises approximately three-quarters of the research supported by the Institute. Moreover, the plan is focused on future research investments. It is not intended to present a comprehensive view of all of the research areas currently receiving NHLBI support.

As with any plan for the future, we expect it to be flexible and dynamic so that the Institute will be able to respond to evolving national needs, Congressional mandates, and advances in scientific knowledge. The opportunities and selected action steps identified in the plan were derived from numerous and extensive discussions and thorough reviews by representatives of the scientific community and by Institute advisory committees and working groups.

Formulation of the Plan

Formulation of the plan began in May 1998 when the Institute assembled a select group of accomplished scientists, the SPARK Working Group (see Appendix), to assist it by identifying those research areas that constitute extraordinary opportunities and merit substantial increases in research investment. The SPARK Working Group developed a research schema entitled "From Genes to Health and Health to Genes" (see Figure 1), that identified four areas of opportunity:

Tissuegenesis/Organogenesis (i.e., ways to repair and replace damaged tissues and organs)

Gene–Environment and Gene–Gene Interactions

Immunobiology

Functional Genomics (i.e., use of new genomic technologies to relate biological function to specific variation of the human genome).

The Institute convened a September 1998 conference organized around the research schema to allow the members of the SPARK Working Group and Institute staff to meet with representatives invited by three of the major professional societies associated with the mission of the NHLBI, i.e., the American Heart Association, the American Thoracic Society, and the American Society of Hematology (see Appendix). Conference participants were divided into working groups to address each area.

Our objective in bringing the groups together was not to elicit their ideas on research directions that address the separate interests of their individual societies but, rather, to ask them to focus on broad research themes that transcend the traditional organ-specific domains within the Institute. In addition to their suggestions for research themes, the participants were also asked to specify those enabling approaches that would be needed to address the areas effectively.

The report of the Conference has been widely disseminated, it has been posted on the Institute's web site (http://www.nhlbi.nih.gov/funding/fromdir/sparkweb.htm), and it has provided the underlying basis for this plan. Institute staff, working with the guidance of the Conference report, then formulated goals and action steps to be addressed over the next several years.

The products of the SPARK process have been complemented by the efforts of the Institute's newly formed Board of Extramural Advisors (BEA) and input from the National Heart, Lung, and Blood Advisory Council (NHLBAC). The BEA is a working group of the Council, consisting of scientists of significant stature in the cardiovascular, lung, blood, and sleep research communities, that is charged with evaluating the NHLBI research and training portfolios on an ongoing basis. Its assessments of proposed research initiatives have been incorporated into this plan.

After review and revision of the plan to reflect the views of the BEA and the NHLBAC, the document was distributed to the major professional organizations related to the mission of the NHLBI and posted on the Institute's web site for public review. Comments and suggestions were solicited from both the organizations and the public, and appropriate revisions have been made.

Organization of the Plan

In 1948, when the U.S. Congress passed a law creating the National Heart Institute, it made clear that our primary focus was to be the health of the American people. We were to conduct "… researches, investigations, experiments, and demonstrations relating to the cause, prevention, and methods of diagnosis and treatment of diseases of the heart and circulation," but they were to be a means to an end, not the end itself. For that reason we have organized this strategic plan largely about the ultimate areas of application of the science. Seven subject areas were identified that encompass the research mandate of the Institute:

Development and Progression of Disease
Diagnosis of Disease
Treatment of Disease
Maintenance of Health Through Prevention of Disease
Translation of Research Results Into Practice
Reduction of Health Disparities
Research Workforce and Research Resources.

Several specific scientific opportunities (i.e., Goals) have been identified within each of the areas. Each of them is considered to be important; no significance is intended by their order of presentation. Several of the goals are interrelated in that research results from one area will often provide important information for related research in another area. Potential FY 2001 initiatives currently being developed and reviewed, as ways to stimulate interest in the identified scientific opportunities, can be found under their corresponding goals. These are the priority steps under consideration for FY 2001. Additional actions to be undertaken in the future that would contribute to realization of the research goals are also included.

Development and Progression of Disease

Goal 1. Identify the genetic variations that predispose individuals to development of cardiovascular, lung, and blood diseases and determine how they interact with environmental factors to cause disease. (see related goals: Development and Progression of Disease, Goal 2; Diagnosis of Disease, Goals 2 and 3)

Gene variations tend to remain unrecognized until they are linked to a widespread or serious disease. They can be the direct cause of a disease or affect disease progression. For example, individuals with asthma who have one form of the beta receptor gene may respond to therapy and progress differently than individuals who have a different form of the gene. Yet, the extent to which genetic variations are involved in disease progression—or in disease prevention—and even the extent to which they occur is unclear. Linking genetic variants to disease is complicated by the compounding effects of such environmental (i.e., nongenetic) factors as neurohormones, stress, behavior, and diet, any of which may disrupt normal gene regulation and thereby lead to disorders in ways that are also not fully understood.

Action:

Potential FY 2001 initiatives:

- **Develop technological methods for high-resolution assessments of an individual's characteristics at the cellular, molecular, and structural levels; identify molecular and biochemical indicators in order to correlate genes with characteristics present in cardiopulmonary, blood, and sleep disorders.** This initiative will stimulate research to find molecular and biochemical indicators (i.e., biomarkers) capable of providing information about a disease at a more fundamental level, and earlier in its development than is presently possible. For example, it is very likely that markers can be found that reflect the presence of coronary disease long before a person experiences a heart attack or that indicate the presence of ongoing lung disease before an individual experiences shortness of breath. Investigators will look for a particular type of cell or a biochemical pathway within a cell as a biomarker of an early stage of disease. Much of the technology necessary to do this still needs to be developed. One area where a biomarker approach will be especially useful is in the study of how inflammation causes or exacerbates cardiopulmonary and blood diseases. Developing a minimally invasive approach to monitor early stages of inflammation, for example, would increase understanding of disease progression and ultimately help researchers to find a way to prevent or control several pulmonary and cerebrovascular diseases. Another application for a biomarker approach might be in assessing lung response to infection with the bacterium that causes tuberculosis, in order to determine factors associated with disease resistance.

- **Identify genetic factors that can determine the severity of sickle cell disease.** Sickle cell disease (SCD) is well understood at the molecular level. However, the marked variability of the clinical manifestations of SCD is not well understood. Some patients experience a series of devastating acute and chronic events that can result in severe end organ damage, including pulmonary damage and stroke, whereas, others have only mild clinical symptoms. The cause of these differences is unclear. Multi-disciplinary basic and

clinical research will be supported to discover new candidate genetic modifiers of SCD severity, as well as to validate current candidate genetic modifiers. The ability to predict the clinical course of SCD should allow greatly improved patient care.

- **Use new technological approaches to analyze the genetic and environmental factors that increase an individual's susceptibility to tissue injury and disease.** Factors affecting tissue injury in such conditions as smoking, chronic obstructive pulmonary disease (COPD), lung cancer, and high blood pressure could be analyzed. For example, the process by which untreated and inadequately controlled hypertension injures blood vessels and contributes to heart and kidney damage is a complicated one. Traditional physiological studies have explained some of the mechanisms by which this occurs. Some of the many remaining questions about individual susceptibility will be addressed by this initiative. They include questions about why individuals with comparable levels and duration of high blood pressure vary greatly in their vulnerability to, and intensity of, organ injury; and what causes blacks in the United States to experience a disproportionate amount of heart and kidney damage and strokes. Recently developed, genetically altered animal models and other modern technologies will be used to study the mechanisms by which genetic and environmental factors cause individual differences.

- **Determine the cellular and molecular mechanisms underlying cell and tissue remodeling in the development of cardiovascular, lung, and blood diseases**. The cell and tissue alterations or remodeling that constitute a key feature of many cardiovascular, lung, and blood diseases are typically associated with modifications in the activities of multiple genes. Organs subjected to stress are initially able to compensate for it, but eventually their cell structure becomes disorganized and the cells themselves begin to malfunction and then die. For example, remodeling in the heart muscle can alter the normal progress of electrical impulses between cells, which can result in first an arrhythmia and then sudden death. In pulmonary fibrosis, lung function is compromised when normal lung tissue is progressively replaced by non-functional fibrotic tissue; and in asthma, airway remodeling can lead to chronic airway obstruction. The cellular and molecular mechanisms responsible for initiation and propagation of remodeling are largely unknown. To increase understanding of remodeling processes in disease progression, investigators will study areas such as characterization of initiating factors; molecular and cellular events in remodeling during disease development; parallels drawn from advances in cell cycling and developmental biology; genetic and phenotypic (i.e., resulting from genetic and environmental influences) risk stratification; and the interplay of genetic, extracellular, and environmental factors that contribute to remodeling.

- **Clarify cellular and inflammatory processes involved in venous thrombosis, and identify clinically relevant familial and environmental factors that predispose an individual to develop venous thrombosis.** Venous thrombosis, the presence of a "clot" in a vein, involves a complex interaction of biologic, behavioral, and environmental factors. It can be inherited or acquired. Better data on subsets of patients with venous thrombosis, correlated with factors that predispose an individual to form blood clots, as well as with the progression of clots, will be valuable in developing specific preventive measures and treatment.

Additional action:

- Produce user-friendly databases on genetic variations, including especially the smallest possible variants, known as single-nucleotide polymorphisms or "SNPs," in both normal and diseased states. Conduct long-term follow-up for detailed understanding of disease progression.

Goal 2. Identify new environmental factors that predispose individuals to development of cardiovascular, lung, or blood disease. (see related goals: Development and Progression of Disease, Goal 1; Diagnosis of Disease, Goals 2 and 3)

Smoking, high-fat diets, and other environmental factors are known to play a role in a large proportion of cardiovascular, lung, and blood diseases. Recently, additional environmental factors have been associated with disease development and progression. Examples include infectious agents (associated with atherosclerosis and asthma); pharmaceutical drugs prescribed for weight loss (valvular heart disease and primary pulmonary hypertension); elevated levels of some substances found naturally in the body, like the amino acid homocysteine (atherosclerosis); low birth weight and obesity later in life (cardiovascular disease and sleep disorders); and psychosocial stress and sleep deprivation (impaired general defense against disease). The role that these and other environmental factors play in the development and progression of disease will be studied. Particular attention will be placed on the genetic factors that cause individuals to be susceptible to environmental influences.

Action:

Potential FY 2001 initiatives:

- **Determine the role of inflammation in the development and progression of cardiovascular, lung, and blood diseases, and translate findings into new approaches for prevention and treatment.** Inflammation, a protective response to foreign agents (e.g., bacteria or viruses) that cause tissue injury, can effectively destroy or "wall off" the injurious agent and aid tissue repair. If the inflammation progresses too far, however, it can actually injure the tissue being repaired. Many cardiovascular, lung, and blood diseases have an inflammatory component. For example, inflammation has been implicated in the development of lesions in atherosclerosis leading to heart attacks, and chronic inflammation is thought to contribute to the development and progression of lung diseases as well as the acute episodes and organ damage common in severe sickle cell anemia. The inflammation that occurs with the restoration of blood flow after therapy for a heart attack is crucial to healing but, if uncontrolled, can contribute ultimately to heart failure. Investigators who have studied inflammation in other systems will be encouraged to identify the largely unknown cellular and molecular mechanisms of inflammation that contribute to the development of cardiovascular, lung, and blood vessel diseases.

- **Investigate the role of infectious agents, and the immune response to them, in the development and progression of cardiovascular, lung, and blood-borne diseases.** Bacterial, viral, and other infectious agents appear to be involved in many cardiovascular, lung, and blood diseases. For example, a link has been established between the cytomegalovirus and atherosclerosis. Viral respiratory infections exacerbate asthma and

may contribute to its development. Recently, two kinds of microorganisms, chlamydia and mycoplasma, have been found in patients with asthma. However, the extent of their contribution to disease development and progression is not known. Investigators with expertise in infectious diseases will be encouraged to collaborate with investigators familiar with cardiovascular, lung, and blood diseases to determine the prevalence and transmissibility of infectious agents associated with cardiovascular, lung, and blood diseases and their mechanism of action. The resultant knowledge will assist in development of prevention and treatment methods and provide new insights into ways to protect the blood supply against emerging infectious agents.

- **Establish a multidisciplinary, multi-institution research program to study immune reactions that develop in patients receiving treatment for blood disorders.** Patients with blood diseases are commonly treated with therapies such as blood transfusions or protein or enzyme replacement. Often, they experience an adverse immune response—that is, their immune system reacts to the foreign substances introduced during treatment in a way that is harmful. For example, patients can produce antibodies against substances in donated blood that can cause a transfusion to be ineffective. Adverse immune responses can cause serious complications and make repeated treatments impossible. Investigators will study how the immune responses develop and how to prevent or counteract them. Hematologists and immunologists will work together, using developing genetic technologies to obtain rapid matches of blood donors and recipients and to analyze genetic variations in patient DNA samples. The scope of this program will initially be limited to treatments for blood diseases, but could be expanded to include treatments used for cardiovascular, lung, and sleep disorders.

- **Determine why only about 15 percent of smokers develop airflow obstruction.** Research will further explore the mechanisms by which smokers develop airflow obstruction. Investigators will assess whether a genetically determined exaggeration of the inflammatory response and proteolytic activity (activity involving the splitting of proteins) is the cause, or whether susceptible smokers have an endogenous mechanism that works against the inflammatory response and proteolytic activity to cause airflow obstruction.

Additional action:

- Standardize methods to use in observational studies for identifying and quantifying exposures to agents thought to be infectious.

- Develop methodologies suitable for population-based studies to identify and quantify acute and chronic effects of infectious agents on airway and vascular walls.

- Determine the effects of nutrition on initiation and progression of cardiovascular, lung, and blood diseases.

- Investigate the effects of sleep deprivation on host defenses.

Goal 3. Identify the mechanisms responsible for transitional events in disease progression.

Many cardiovascular, lung, and blood diseases and sleep dysfunctions are chronic conditions that progress, in stages, until they reach an acute clinical event such as a heart attack, a stroke, or lung failure. Research to determine the mechanisms by which genes that produce defective products, or normal products at the wrong time or place, cause cell death, organ dysfunction and, eventually, patient death can be expected to provide clues to ways to interrupt this sequence of events. This, in turn, may lead to new approaches to disease prevention and treatment.

Such sequences of events may occur in sickle cell disease, atherosclerosis, and heart failure. For example, the segment of DNA known to control activation of one specific gene may also control the way that gene responds to the physical or "shear" stress caused by one cell sliding relative to another. Shear stress can change the structure of the cells that line the cavities of the heart and blood vessels. This indicates a potential link between certain genes, regions of altered shear stress in blood vessels, and, ultimately, susceptibility to atherosclerotic plaque development, progression, and rupture. It is possible that altering the sequence of events that begins with gene activation could prevent some disease development. Recent studies have demonstrated that shear stress can help protect against the conditions leading to atherosclerosis or endothelial damage caused by sickle cells. An indication that disease progression may in some cases be reversible is provided by reports of improved heart structure and function in patients with heart failure who receive circulatory support from a left ventricular assist device.

Action:

- Identify priority research areas in the pathogenesis of cardiovascular and blood disease progression.

- Define the genetic determinants involved in the normal and pathologic conditions that induce disease progression.

Goal 4. Determine the relationship between mechanisms of cellular development and differentiation and the establishment of disease.

Studies of development at the molecular level, including studies of the molecular signals involved in the growth and development of embryos, will shed light on the similarities and differences between processes of development and processes of cellular injury and repair. In addition, studies about cell and organ aging will increase understanding of the disease process.

Action:

Potential FY 2001 initiatives:

- **Generate mouse models useful in new approaches to studying the development of cardiovascular, lung, and blood disease.** Mouse models in which genes are inactivated ("knock-out" models) or in which a mutated form of a gene is substituted ("knock-in" models)

are providing important information about maturation and disease development. Techniques will be refined to allow the development of knock-out and knock-in mouse models in which a gene can be inactivated or replaced in specific organs, tissues, or cells and at any time during the life of a mouse. This will allow investigators to study mouse models of human diseases that occur during adolescence, middle age, and old age, as well as during embryonic development, and to study more subtle and complex forms of diseases. Also, inducible transgenic animal models (in which animals are produced from a genetically manipulated egg or embryo by a technique involving injecting DNA fragments from another species into the nucleus of a fertilized egg) will be used to turn genes on and off at specific stages of development to study chronic disease.

- **Determine the role of "cellular aging" in the progression of specific cardiopulmonary diseases.** Investigators will study the role, in specific human diseases, of the pathways and gene products known to be involved in cellular aging in lower organisms and mammalian cells. They will analyze animal models of aging to determine if they show an increased susceptibility to specific cardiopulmonary diseases. Studies will be undertaken to explore the possibility that organs may age at different rates and investigate how this relates to organ-specific disease susceptibility. The characteristics of aging cells in the vascular system, lung, and heart will be described in detail, and their relationship to characteristics of diseased cells will be elucidated.

- **Create a multidisciplinary research program to develop a systematic understanding of the complex interactions that underlie cell, tissue, and organ function and the alterations that produce disease.** The goal of this initiative is to provide the infrastructure necessary to integrate varied disciplines and approaches in order to discover properties of the complex systems that affect disease development. Building on knowledge that is arising from molecular genetics, this research will look at disease as a complex system, using mathematical modeling to suggest approaches to physiology at the molecular level, as well as at the level of the whole organism. An example of the systems approach to studying cardiovascular disease would be to define the role of the large number of genes involved in human cardiac function and to examine their relationships to vascular phenomena, involving such influences as sex hormones, aging, and psychological stress in the development of atherosclerotic changes and their clinical sequence. The centers of research will include systems analysts, mathematicians, and engineers, as well as clinicians and biomedical scientists with experience in disease research.

Additional action:

- Stimulate new research strategies to identify and characterize mechanisms of prenatal programming that result in chronic cardiovascular, lung, and blood disease later in life.

- Conduct studies to determine the mechanisms by which nutritional supplementation enhances development and repair.

- Identify biomarkers for cardiovascular, lung, and blood diseases that will enable accurate monitoring of the development and progression of pathogenesis and therapeutic response.

- Define the contribution of angiogenesis (the formation of blood vessels) and other forms of microvascular remodeling in the development of cardiovascular and vascular diseases.

- Determine whether blockers or stimulators of apoptosis (programmed, nonpathological cell death) can be used to alter cell fate in development of disease.

Diagnosis of Disease

Goal 1. Develop and validate new methods of detecting inflammation-associated cardiovascular, lung, and blood diseases. (see related potential FY2001 initiatives: first initiative under Development and Progression of Disease, Goal 1; and first initiative under Development and Progression of Disease, Goal 2)

Inflammation is a component of many cardiovascular, lung, and blood diseases (e.g., atherosclerosis, asthma, sickle cell disease). Although scientists have identified certain indicators of inflammation that are related to them, many of the indicators can also be elevated in other unrelated chronic inflammatory conditions. Even without this potential for confusion, it is unclear how effective the currently available indicators are in detecting inflammatory cardiovascular, lung, and blood diseases. Simple, reliable ways of detecting the presence and assessing the extent of inflammation related to them will permit earlier diagnosis that may enable more effective treatment. They will also allow investigators to determine whether therapies to control inflammation are effective in reducing morbidity and mortality from cardiovascular, lung, and blood diseases.

Action:

Potential FY 2001 initiative:

- **Find and validate new biochemical markers and develop imaging techniques to identify and measure the inflammatory response in cardiovascular and lung tissues and blood.** New biochemical markers of inflammation will be sought that are reliably elevated only in the presence of cardiovascular, lung, or blood disease. Such markers will permit investigators and clinicians to predict onset of disease and to monitor disease progression and response to therapy. Potential markers include materials produced by defective or damaged genes, injured body tissues, or infectious agents; they might be detected in the blood, urine, sputum, bronchoalveolar lavage fluid, expired air, saliva, or even hair of patients. New imaging techniques will also be developed that will permit investigators and clinicians to observe directly how cardiovascular and lung tissues and blood are affected when inflammation occurs. Included among them might be imaging probes and contrast agents linked to antibodies visible by x-ray or reporter molecules that undergo chemical changes in areas of inflammation, as well as conventional imaging techniques such as ultrasound and magnetic resonance imaging (MRI).

Additional action:

- Identify infectious, metabolic, and genetic factors most likely to cause or sustain inflammation.

- Develop therapies that reduce inflammation and test their effects.

- Determine whether anti-inflammatory therapies can reduce morbidity and mortality in patients with cardiovascular, lung, and blood diseases who also show evidence of active inflammation.

Goal 2. Apply genetic and genomic technologies to the diagnosis of cardiovascular, lung, and blood diseases. (see related goals: Development and Progression of Disease, Goals 1 and 2; Diagnosis of Disease, Goal 3)

New technologies, including those that allow analysis of the activity of thousands of genes simultaneously, will help investigators increase understanding about how genetic variations can affect the development of cardiovascular, lung, and blood diseases. Investigators will search for genes that cause an individual to be more susceptible to a disease, as well as genes that help protect a person from developing a disease. They will also explore the effects on disease development and progression of interactions among genes and interactions between genes and environmental influences. The objective is to enable clinicians to identify individuals at risk for disease before they develop symptoms; to assist them in designing more effective, individualized treatments; and to provide them with guidance as to how disease can be prevented.

Action:

Potential FY 2001 initiatives:

- **Establish a fine-mapping and sequencing laboratory to facilitate gene discovery.** NHLBI-supported researchers are identifying large regions of the human genome that contain genes associated with cardiovascular, lung, and blood diseases and sleep disorders. Fine (i.e., more precise) mapping can be accomplished using several genetic and genomic technologies to narrow those regions known to contain disease-associated genes and, ultimately, to identify the genes themselves. A specialized fine-mapping and sequencing (i.e., determining the order of the chemical subunits of DNA) facility will be a cost-effective approach that will serve to increase the rate of gene discovery, while providing greater control over intellectual property rights issues and data-sharing policies and enabling improved quality control.

- **Establish a national network of human twin research centers.** Twins constitute an ideal context for studying interactions between genetic and nongenetic influences on disease development because factors such as age, intrauterine and early family environment, and background genotype can be controlled. The objective of the centers will be to collect longitudinal data on observable traits, including weight and presence of disease, as well as blood and DNA samples, from large numbers of twin pairs. This resource will enable researchers to determine the effect of specific genes on disease development under different environmental situations and in the presence or absence or other genes. It will also facilitate investigations of the effect of environmental factors such as drug treatment on persons with different genotypes. The network offers several advantages over existing twin studies in that it will provide access to longitudinal data on larger numbers of twin pairs and will include multiple racial/ethnic groups.

- **Investigate diagnostic and therapeutic approaches for congenital and acquired pediatric cardiovascular conditions from fetal life into adulthood.** Approximately 32,000 infants are born each year with congenital cardiovascular malformations, one of the leading causes of infant mortality. In addition, acquired pediatric cardiovascular conditions, including arrhythmias, inflammatory conditions, cardiomyopathies, hypertension, and

hyperlipidemia affect several million children and adolescents. Treatment of congenital and acquired pediatric cardiovascular disease involves drug and surgical therapies. Yet, most standard therapeutic drugs have not been tested in randomized controlled trials in children. Surgical correction has side effects in children about which much is still unclear. A collaborative network of ten to 12 clinical research centers and a data coordinating center will evaluate standard and new diagnostic and therapeutic strategies in pediatric cardiovascular medicine. The network approach can also promote training of investigators in pediatric clinical research and provide a way to ensure rapid dissemination of research findings.

Additional action:

- Develop studies to identify gene function and disease-causing mutations in genes associated with cardiovascular, lung, and blood diseases and sleep disorders.

- Promote development and improvement of microarray and other genetic technologies.

- Promote interdisciplinary training to enable investigators from a range of disciplines to contribute to research in genetics/genomics.

Goal 3. Identify and assess new risk factors for cardiovascular, lung, and blood diseases. (see related goals: Development and Progression of Disease, Goals 1 and 2; Diagnosis of Disease, Goal 2)

Despite previous success in identifying risk factors for cardiovascular, lung, and blood diseases, including long-recognized, extensively studied ones (e.g., smoking, high-fat diet, hypertension, diabetes) and more recently discovered, less-understood ones (e.g., inflammation and sleep apnea), population studies suggest that still other, as-yet-unidentified factors also exert a strong influence on the incidence of cardiovascular, lung, and blood diseases. For example, about half of all heart attacks are not correlated with any known risk factors, and the reasons for much of the recent increase in the incidence of asthma in the United States are unknown. A combination of factors such as a variation in a gene, perhaps coupled with taking a drug at a particular stage of life, could predispose an individual to develop a disease later in life. Identification of new risk factors and development of technological approaches to evaluate them are needed to predict disease susceptibility more reliably.

Action:

Potential FY 2001 initiative:

- **Develop reliable methodologies to assess the relative contributions of genetic and environmental factors in elevating risk.** Techniques for relating small genetic variations to increased disease susceptibilities will be developed. The interaction of more than one gene, and of variants of a gene, with external influences (e.g., therapeutic drug use) will be examined. Situations where more than one risk factor is involved will also be investigated.

Additional action:

- Examine clinical and population databases, both retrospectively and prospectively, to evaluate potential indicators of risk for developing disease.

- Stimulate research to develop indicators of risk in specific diseases, particularly diseases with high public health impact.

- Convene a multidisciplinary group of experts to review unresolved questions of public health importance about cholesterol-lowering therapy.

- Apply new “chip” technology (tiny chips that contain genes known to be associated with cardiovascular, lung, and blood disease risk) to screen patient DNA samples in controlled clinical trials to correlate genetic risk factors with clinical events (e.g., heart attacks).

- Develop a risk factor profile (using genomic technology) for clinical trial populations and other selected populations at risk for developing cardiovascular, lung, and blood diseases, and compare it with the risk factor profile developed from the Framingham Heart Study (a long-running epidemiological study of cardiovascular disease).

Treatment of Disease

Goal 1. Develop an integrated program of basic and clinical studies in gene therapy that will enable rapid application of findings to human research.

Gene therapy is likely to be used soon to treat patients with cardiovascular, lung, and blood diseases. Good candidates for gene therapy are diseases influenced by a single gene (e.g., sickle cell disease) and conditions that can be corrected by temporary activation of an inserted gene (e.g., restenosis, pulmonary hypertension, or acute lung injury). Animal models of human disease are not always sufficient to test the efficacy of experimental therapies—in cystic fibrosis or primary pulmonary hypertension, for example, animal models do not adequately mimic the human disease—so research environments are needed that not only support basic research in gene therapy technology, but also enable application of basic research findings to human pilot studies. Moreover, clinical studies can help to refine research questions to be addressed by nonclinical investigation, and even identify new ones.

Action:

Potential FY 2001 initiative:

- **Establish a multidisciplinary, multi-institution program of basic and clinical studies in gene therapy to facilitate the application of basic findings to new approaches to treatment.** The program will be based on the collaboration of basic investigators involved in molecular biology, biochemistry, and physiology with clinicians skilled in applying gene therapy to cardiovascular, lung, and blood diseases. The program's research centers will share facilities for resources and services, such as viral vectors (viruses used to insert genes into human cells), animal models, cell-imaging and cell-isolation capabilities, toxicology and immunology studies, and biostatistics expertise. The program will support pilot and feasibility projects, and establish training programs for physician-scientists in applying basic research in gene therapy to the clinical setting (e.g., training for performing phase I and II clinical trials).

Additional action:

- Establish centralized resource facilities to provide such services as safety testing in animals or large-scale production of materials necessary for gene therapy protocols.

- Conduct preclinical studies (e.g., toxicology studies).

Goal 2. Develop and use genetic and genomic approaches to identify the genetic basis for individual therapeutic and adverse responses to drugs used in cardiovascular, lung, and blood diseases, and develop new therapeutic agents and targets.

Individual differences in response to a drug may be due to genetic differences in how the body handles the drug (e.g., variations in distribution, metabolism, excretion) or in how the drug affects the body (e.g., differences in the body's chemical receptors, enzymes, and intracellular

pathways). Research using genetic and genomic technologies, such as those resulting from the Human Genome Project, will help investigators learn more about the genetic basis of individual therapeutic and adverse responses to drugs. Then investigators will develop ways to identify and predict the responses. At the same time, this technology will be used to study the molecular pathways by which complex diseases develop and progress. Gene products (i.e., substances produced by active genes) that are involved in cardiovascular, lung, and blood diseases are likely to be discovered, thereby helping scientists to identify new targets for treatment.

Action:

Potential FY 2001 initiatives:

- **Identify genetic factors and mechanisms that affect how patients respond to drugs.** Advances in molecular genetics and the tools and resources developed by the Human Genome Project will be used to investigate genetic differences that influence how patients respond to drugs used in cardiovascular, lung, and blood diseases. Studies ancillary to ongoing clinical studies could be a cost-effective way to investigate, for example, variations in response to antihypertensive medications and drugs used in treating asthma, or the genetic basis of drug-induced aplastic anemia.

- **Delineate components of the molecular pathways by which complex diseases develop and progress in order to identify targets for treatment.** State-of-the-art molecular genetic technologies (e.g., gene trapping in response to specific stimuli) will be used to study complex chronic cardiovascular, lung, and blood diseases. These diseases result over time from factors ranging from established risk factors (e.g., hypercholesterolemia, smoking, diabetes, hypertension) to emerging potential risk factors (e.g., infections). The molecular pathways by which these risk factors cause disease will be identified. Another likely result will be discovery of gene products involved in the disease processes, leading to identification of new targets for treatment. This initiative will include establishment of shared facilities, possibly at multiple regional sites, to provide investigators access to genomic technologies.

- **Reduce the current 20-30 percent incidence of restenosis.** Restenosis (recurrent narrowing of vessels after correction) has been decreased, but not eliminated, by use of stents (devices to keep the vessels open) following angioplasty. In animal models, several gene transfer strategies have decreased restenosis. This initiative will support research and development combining stent and gene/drug delivery technologies in two major areas: development of improved biocompatibility of stent designs and materials to reduce inflammatory and proliferative (i.e., restenosis-inducing) responses and development of antithrombotic and antiproliferative agents (including conventional drugs and gene therapy) to be delivered to the vascular wall cells.

Additional action:

- Improve methods of tissue-specific delivery of drugs and genes.

- Identify components of the biological pathways that contribute to complex chronic diseases of the cardiovascular, pulmonary, and hematologic systems in order to develop targets for treatment.

Goal 3. Improve the outcome of heart and lung transplantation and increase the supply of donor organs.

Heart and lung transplantation is hampered by a high rate of acute and chronic rejection of the transplanted organ, as well as by a shortage of human organ donors. Better methods of organ preservation prior to transplantation will avoid injury to the organ that can cause problems after transplantation. In addition, better ways of suppressing a patient's immune system, as well as inducing immune-system tolerance for the transplanted heart or lungs, will free transplant patients from life-long immunosuppressive drug regimens that are not always effective and can have serious side-effects. Using animal organs to replace failed human ones (xenotransplantation) would increase the supply of organs, but a number of immunologic, physiologic, and ethical issues must be addressed before this could be considered a feasible option.

Action:

Potential FY 2001 initiative:

- **Clarify the underlying causes of chronic rejection, the primary cause of death for long-term heart and lung transplant survivors.** Among 5-year survivors, an estimated 60 percent of heart recipients and 60 to 80 percent of lung recipients suffer from chronic rejection—a gradual, progressive loss of function of the transplanted heart or lung. Multidisciplinary, interrelated studies will be supported to increase understanding of the cellular and molecular basis for chronic rejection.

Additional action:

- Hold a workshop on post-transplant heart and lung complications.

- Develop better methods of organ preservation.

- Clarify the mechanisms of xenotransplant rejection and develop strategies to overcome it.

- Establish a network of transplantation centers to identify and address critical immunobiological questions, support basic and clinical studies, enable the rapid implementation of basic research findings into patient-oriented research, and provide information and clinical consultation on transplantation.

- Support core facilities to develop transgenic pigs for use as organ donors, to generate gene transfer techniques to modulate or suppress immune response, and to identify approaches to reduce injury to donated organs due to ischemia (i.e., blood deficiency) and reperfusion (i.e., subsequent therapy to restore the blood supply).

Goal 4. Improve the efficacy and utility of hematopoietic stem cell transplantation.

Hematopoietic stem cells are cells that are capable of continually replenishing all of the components of the blood. Hematopoietic stem cell transplantation (HSCT) can cure patients with a variety of blood-related diseases, bone marrow failure syndromes, blood-related malignancies, and genetic disorders. However, a variety of problems presently limit the applicability of this procedure. Many more diseases will be treatable with HSCT once progress is made in formulating less toxic pre-transplant regimens, reducing complications (e.g., graft-versus-host disease and immune system problems), and developing a reliable test for stem cell engraftment (i.e., the successful transplantation of cells). The benefits of HSCT will also be available to more patients when transplants can be performed from less well-matched donors.

Action:

Potential FY 2001 initiatives:

- **Establish a network of transplant centers to conduct clinical studies of new therapies in HSCT, and to conduct full-scale, definitive studies when warranted by initial results.** Some of the challenges that could be addressed by the network are developing less toxic conditioning regimens for patients with non-malignant disease, improving cell manipulation techniques to enhance engraftment, finding effective treatment for patients who develop graft-versus-host disease, and addressing the use of stem cells for gene therapy. None of these issues could be resolved conclusively in a clinical trial conducted in one or two institutions. The network of transplant centers will facilitate collaboration among several sites, and provide the infrastructure to enable promising treatments to be moved quickly from an initial study into a definitive clinical trial. Access to more patients and different patient populations will be improved, and a resource component of the network will provide easy access to clinical-grade reagents (substances used to detect or measure other substances by producing a chemical reaction).

- **Develop tests to evaluate both quantitatively and qualitatively the sustained engraftment and self-renewal capacity of human hematopoietic stem cells.** Currently, patients with a variety of blood-related diseases and disorders are transplanted with hematopoietic stem cell preparations about which the engrafting potential and maintenance of the stem cell pool prior to transplant cannot be accurately assessed. Widely used laboratory tests are not accurate for predicting engraftment potential in the transplanted individual. Animal models engrafted with human stem cells have been developed, but have many limitations. New and/or improved approaches will be developed that allow tests within the living body to evaluate potentials for successful stem cell engraftment and self-renewal.

Additional action:

- Support efforts to develop, maintain, and distribute a standard source of hematopoietic stem cells so that different laboratories can compare their tests for engraftment.

- Develop a reliable test to predict engraftment of human hematopoietic stem cells.

- Hold a workshop to discuss the needs of transplant physicians and basic scientists for expanded hematopoietic stem cell production.

- Develop improved methods of umbilical cord blood collection and storage. Investigate new uses for umbilical cord blood, such as cell expansion, gene therapy, and development of new tissues.

- Develop methods to increase laboratory production of hematopoietic stem cells for clinical use.

- Develop approaches to induce immune tolerance (i.e., ways to cause the immune system to become nonreactive to one or more antigens).

- Develop tests to predict the development of graft-versus-host disease (i.e., an immunological attack mounted by the donor cells against the patient's body).

- Study immune function in patients after transplantation.

- Investigate methods of inducing tolerance to specific antigens, indicators of tolerance and indicators of secondary graft failure, and approaches to translating the results of this research into clinical use.

Goal 5. Develop the scientific underpinning necessary to be able to repair or replace damaged tissues and organs.

Diseased tissue and organs in conditions such as end-stage heart disease, chronic lung disease, and aplastic anemia often disable otherwise healthy individuals. Advances in molecular, cellular, and developmental biology are ushering in the day when it will be possible to use cells to repair diseased or damaged heart, lung, or blood tissue, or to grow replacement tissues and organs (tissuegenesis/organogenesis). Stem cells—cells capable of giving rise to other more specialized cells—might someday be used to improve heart and lung function, or to deliver growth factors and other therapeutic agents. Once researchers have identified genes and cells responsible for early development of the heart and lungs, they might be able to activate specific genes to replicate whole organs or identify methods to remodel damaged tissue (e.g., to change lung fibrotic tissue to normal alveolar tissue). To get to this point, further research is needed to understand the developmental biology of the heart and lungs, to devise methods for growing and differentiating stem cells, and to find ways to grow tissues and cells to specific requirements.

Action:

Potential FY 2001 initiative:

- **Stimulate multidisciplinary research to overcome known barriers to tissuegenesis/organogenesis.** This initiative will support multidisciplinary research in the following areas: improving techniques to supply growing tissue with blood vessels, further elucidating the regulation of gene activation, increasing knowledge about the structure and function of the matrix made of proteins that surrounds cells (histoarchitecture), further

clarifying the process of cell and tissue injury and repair; and increasing understanding about the factors that control stem cell and organ development and differentiation.

Goal 6. Obtain information on disease development and treatment options that would lead to evidence-based treatment decisions for patients with rare cardiovascular, lung, and blood diseases. (see related goal: Translation of Research Results into Practice, Goal 2)

A number of cardiovascular, lung, and blood diseases affect only a few hundred to several thousand people each year, but collectively represent a significant public health problem. Often, specialists at individual medical centers see only a few patients with any one rare condition. The development of evidence-based medicine is essential for the care of these patients. Physicians need a systematic way to share information on diagnostic and treatment strategies and results, so that their decisions are based on scientific evidence from as many patients as possible. A network of patients is needed to be able to perform meaningful clinical studies because of the limited numbers of patients that may be available at any given medical center.

Action:

Potential FY 2001 initiative:

- **Convene experts to begin the process of developing networks of patients with rare cardiovascular, lung, and blood diseases.** Topics to be addressed include the following:

  - Establishing systems for centralized electronic data acquisition and dissemination in order to develop “virtual” patient cohorts. These cohorts will help physicians develop common diagnostic criteria and will form the basis for multicenter studies of therapeutic interventions and monitoring of short- and long-term outcomes.

  - Supporting retrospective and prospective clinical trials.

  - Involving managed care organizations, primary care physicians, and professional societies.

  - Training health care personnel in, for example, electronic data base management and design of studies in small populations of patients.

Additional action:

- Support development and operation of databases and registries for patients with rare cardiovascular, lung, and blood diseases.

- Conduct retrospective and prospective clinical studies of rare cardiovascular, lung, and blood diseases.

Maintenance of Health through Prevention of Disease

Goal 1. Increase understanding of how behavior affects the development of risk factors and determine how to combine lifestyle changes and medical management to prevent or reduce them.

Morbidity and mortality from cardiovascular and lung disease would decrease significantly if known risk factors could be controlled or prevented. A better understanding of how some lifestyles contribute to risk factor development would allow more effective interventions to be designed. The effects of years of a high-fat diet or smoking are obvious. But other questions remain unanswered, such as what causes blood pressure and weight to increase with age; how genes, environment, and behavior interact to affect development of risk factors; and how nutrition, weight, sleep, and stress early in life affect risk development later on. Much is known about behaviors that are healthful and those that are not, but more successful methods are needed to help people replace unhealthful behaviors with healthful ones in the long-term. Improved methods are also needed to combine medical intervention and lifestyle changes to treat patients. For example, antihypertensive medications are highly effective in controlling blood pressure, but increased physical activity, weight loss and, a diet high in fruits, vegetables, and low-fat dairy products can also contribute to lower blood pressure. Researchers will study how best to combine these several approaches.

Action:

Potential FY 2001 initiative:

- **Determine whether high intake of sodium during early infancy is associated with higher level of blood pressure later in life.** This initiative is based on animal and human studies that show some dietary components consumed early in life may affect the levels of subsequent cardiovascular disease risk factors.

Additional action:

- Examine environmental and behavioral influences on risk factor development by incorporating high quality measurements into observational epidemiologic studies.

- Analyze the relationship between behavioral and environmental factors early in life and cardiovascular disease risk factors later in life.

- Test interventions for maintaining long-term healthful behaviors.

- Test interventions for preventing the age-related rise in cardiovascular disease risk factors (e.g., rise in blood pressure during adulthood) and the increase in risk factor levels that occurs at key transitional times in life (e.g., reduction of physical activity during adolescence).

- Test whether combined medical and lifestyle management of cholesterol levels and hypertension is more effective than medical management alone, and whether it can be sustained for an extended period of time.

Goal 2. Continue to improve blood transfusion safety.

An estimated 3.8 million Americans receive blood transfusions annually. Rigorous scrutiny of blood donors and the screening of donated blood has significantly reduced morbidity and mortality due to transfusion-associated infectious agents. Transfusion practices now carry a small, but still unacceptable, risk of infection from transfusion-transmitted viruses. Procedures are currently available, such as the use of photochemicals, that destroy virus infectivity with minimal adverse effects on the blood components. Cost-efficient technological advances are needed to permit the use of photochemicals, as well as other inactivation procedures, in large-scale blood centers.

Action:

- Continue research to inactivate viruses and other transfusion-transmitted pathogens in blood components while maintaining the therapeutic effectiveness of these components.

- Determine reasons why "at-risk" blood donors continue to donate.

- Investigate how to motivate "low-risk" populations to start (or to continue) donating blood or marrow.

Goal 3. Develop more comprehensive dietary recommendations to improve cardiovascular health.

Advice about what to eat is everywhere—from health messages in newspapers to food labels in grocery stores. Yet a number of important nutritional issues with implications for cardiovascular health remain unresolved. For example, it is not clear what dietary components should replace saturated fats so that optimal cholesterol levels will result. Also unknown are the proportions of proteins, fats, and carbohydrates in the diet that lead to healthy blood pressure levels. It has been speculated that antioxidants slow the development of atherosclerosis, but how diets should be modified to increase antioxidant levels remains to be determined. In addition, research is needed on the effects of dietary components on subclinical disease (disease in its early stages, even before symptoms are detectable) and how the diets of special populations affect their disease risk.

Action:

Potential FY 2001 initiative:

- **Evaluate long-term effects of diet.** Intervention studies will compare the long-term (at least 3 years) effects of at least four diets that vary in proportions of proteins, fats, and carbohydrates. The effects of the diets on a number of risk factors assessed as a group, rather than individually, will be evaluated; the risk factors of interest include blood lipids, blood pressure, glucose tolerance, weight, homocysteine (an amino acid), Lp(a) (a

lipoprotein correlated with increased risk of heart disease at very high levels), and immune function. The effect of the diets on some measure of subclinical atherosclerosis will also be evaluated. Dietary effects on specific population subgroups, defined by race, sex, age, and risk factor levels, will be assessed.

Additional action:

- Improve methodology currently used in dietary research, including self-reporting methods and biological indicators of the effects of variations in diet.

- Study dietary effects on development of subclinical disease in animal models.

- Study gene-diet interactions in animal models.

- Determine the efficacy of dietary components, at various points in the life cycle, in reducing development of subclinical disease and cardiovascular disease risk factors.

Translation of Research Results into Practice

Goal 1. Examine factors that influence, and methods to increase, the dissemination and implementation of preventive interventions.

Exercise, low-fat diets, abstinence from smoking, good sleep habits, and regular blood pressure checks are some of the behaviors routinely recommended by health professionals because of their known effectiveness in preventing health problems. Nonetheless, many people still have not heard these recommendations and others ignore them. Members of minority groups and low-income individuals have few resources with which to learn about these recommendations. And for many, maintaining healthful behaviors over the long-term is difficult. Behavioral studies are needed to identify the determinants of successful dissemination and implementation of prevention recommendations in community and health care settings, and to develop and test interventions that promote adoption of healthful behaviors.

Action:

Potential FY 2001 initiative:

- **Support studies to improve implementation of current recommendations for preventing cardiovascular and lung diseases and risk factors**. Investigations are needed on the factors that enhance, as well as impede, implementation of prevention recommendations. Strategies for increasing implementation, including ways of presenting recommendations to physicians and to the public, as well as ways of communicating to patients and physicians the overall level of risk a person has of developing a specific disease (e.g., formulas based on measurement of risk factors) need to be developed and tested.

Additional action:

- Organize a workshop to explore a potential role for the media in disseminating information about behavior recommended for preventing disease and risk. One approach might involve direct public education using the plot and dialogue of popular radio and television shows (e.g., comedies, cartoons, soap operas) to teach healthy behavior.

- Initiate observational and interventional studies in community and health care settings to assess and improve dissemination and implementation of prevention promotion programs for the general public and for patients.

- Support observational and interventional studies that combine individual and community approaches to promote behavior change for the general public and for patients.

- Conduct observational studies that examine the determinants of long-term maintenance of health-promoting behaviors and interventional studies that test their effectiveness in ensuring long-term maintenance of health-promoting behaviors.

Goal 2. Examine factors that influence, and methods to increase, the dissemination and implementation of evidence-based clinical treatment guidelines in medical practice. (see related goal: Treatment of Disease, Goal 6)

The NHLBI currently supports evidence-based clinical practice guidelines on hypertension, high blood cholesterol, asthma, and obesity. The guidelines are based on a systematic review of current scientific literature and incorporate key messages for clinical practice. The lag between publication of research findings demonstrating the effectiveness of clinical strategies and development of clinical guidelines and their adoption into clinical practice has not diminished appreciably over the last 20 years. Traditional dissemination methods, such as publication in medical journals and distribution of printed materials, has resulted in more widespread adoption of clinical treatment guidelines by specialists, but not by primary care providers. Advances in communication and information technology can promote more rapid dissemination of research results and more widespread adoption of clinical treatment guidelines in medical practice.

Action:

Potential FY 2001 initiatives:

- **Develop computerized systems to support evidence-based clinical practice in the treatment of asthma, heart disease, and hypertension.** A computerized system to support evidence-based clinical practice treatment should be designed and tested in managed care organizations (MCOs). MCOs offer access to large numbers of patients and an existing infrastructure that includes patient databases and computerized office systems. Components of the system could include patient records that prompt and monitor clinician adherence to guidelines at the point of patient care, generation of individual patient care plans in which the computer program helps the clinician tailor guidelines to specific patient needs, integration of services (e.g., links among all members of the health care team), networking with community medical leaders to enhance motivation and provide consultation, linkages with scientific databases and national science-based programs, and performance reports. If successful, the system could be tested in different health care settings that serve diverse patient populations.

- **Create a new clinical practice award for managed care organizations to provide financial support to develop and evaluate office systems that increase the use of evidence-based clinical treatment guidelines.** Managed care organizations will develop or modify procedures and systems that accelerate dissemination of research findings and lead to more widespread use and monitoring of clinical treatment guidelines in patient care. Programs and procedures that are developed will be evaluated, and successful ones will be disseminated to other managed care organizations.

Additional action:

- Test advanced computer technology and bioinformatics systems that can bridge the gap between scientific research and clinical practice for treatment of cardiovascular, lung, and blood diseases.

- Support studies in clinical settings to assess and improve dissemination and implementation of proven cardiovascular, lung, and blood disease and sleep disorder treatment approaches.

- Develop and test strategies for accelerating translation of research into changes for primary care practice (e.g., video conferences, “virtual clinics” or “virtual grand rounds”, interactive continuing medical education, visitor exchanges within regional communities between colleagues, professors, and trainees).

- Develop an information network to promote dissemination of research results from future NHLBI-supported clinical research programs and facilitate translation of results into clinical practice.

Goal 3. Facilitate the translation of basic research ideas to clinical investigation.

New tools are needed to accelerate application of basic research findings to human studies. Special efforts should focus on training more clinically oriented investigators, improving techniques for diagnosing rare diseases, and reducing the cost of key materials needed to conduct research.

Action:

Potential FY 2001 initiative:

- **Establish centers to increase accessibility to resources necessary to test research findings about genetic diseases in a clinical setting.** The resource centers could be at centralized locations, or they could be “virtual centers.” Examples of centers that would increase accessibility to resources include:

    - a research center to diagnose genetic disorders and predict treatment response that would also provide clinical investigators with reagents for diagnostic tests and become a repository of information on patients with genetic disorders.

    - a center to produce at reasonable cost clinical grade reagents for investigators, including vectors (usually viruses used to insert genes into human cells), cytokines (proteins that under certain circumstances act as intercellular mediators), and monoclonal antibodies (antibodies derived from a single cell).

    - a center specializing in bioinformatics (a field concerned with developing techniques -- computational methods, computer tools, and information systems -- to help manage and interpret large amounts of molecular biology data).

Additional action:

- Develop reliable indicators molecular, biochemical, or imaging-based to detect specific clinical outcomes.

- Develop improved procedures for diagnosing rare diseases.

- Develop efficient, less costly, centralized facilities for diagnosis.

- Train clinical investigators to perform research that translates basic ideas into human studies by providing training opportunities at entry and mid-career levels, and by using training modules on the Web.

- Develop expanded internet technologies to mesh new research findings with existing relevant clinical networks.

Reduction of Health Disparities

Goal 1. Develop and test interventions to improve health behaviors and outcomes in individuals of lower socioeconomic status (SES) and in minority individuals, as well as to improve health-care seeking and delivery in these populations.

Individuals who are of lower socioeconomic status (SES) or of minority status have worse health, eat higher fat diets, smoke more, and are less physically active than individuals of higher SES or nonminorities. They are also more likely to have high blood pressure and diabetes, to be overweight, and to experience higher rates of disability and death from cardiovascular disease, asthma, and sleep disorders. Environmental conditions (e.g., unavailability of low-fat foods at neighborhood grocery stores, lack of convenient places to be active, and absence of supportive policies in the workplace) have an especially strong influence on behavior in low-SES and minority groups. Many of these population groups also face barriers to health care access. Some of them, such as inconvenient distance to health care facilities, affect all population subgroups whereas others, notably inability to speak English, are specific to selected subgroups.

Action:

Potential FY 2001 initiatives:

- **Develop and test worksite interventions to reduce risk of cardiovascular, lung, and sleep disorders.** Worksites with large populations of minority or low-SES workers will be targeted. Interventions will involve environmental approaches to behavior change (such as altering organizational practices, policies, and regulations or offering economic incentives) and may be combined with health education or other individual approaches. The relative effects of interventions to promote health behaviors and outcomes will be assessed by SES status, race/ethnicity, and gender.

- **Support technology development to overcome disparities in health-care seeking and delivery.** Advances in communications and information technology will be used to develop new approaches to communicating with disadvantaged groups about health care issues. Technology will enable individual members of disadvantaged groups to reach health care providers despite problems due to distance, language, or culture. In addition, relatively inexpensive technologies to support “patient empowerment” strategies, including home blood glucose monitoring and coagulation monitoring, could be developed that would be readily available to all population subgroups. Such approaches need to be developed further and evaluated for their potential contribution to overcoming disparities in health-care seeking and delivery among population subgroups.

Additional action:

- Support collaboration with the many ethnic professional medical organizations across the country in areas such as selecting population groups for study, improving dissemination of information, increasing understanding about the ways that various cultural practices can affect health behaviors and outcomes.

- Incorporate into observational epidemiologic studies measures of potential environmental influences on health behaviors and outcomes, as well as measures of health-care seeking and delivery.

- Develop effective interventions that can be implemented in disadvantaged populations.

Goal 2. Improve understanding about mechanisms that cause diseases to develop and manifest themselves differently in women and men.

Although the incidence of major cardiovascular disease increases with age in both men and women, the increase typically occurs 10 to 15 years later in women than in men. The conventional explanation is that estrogen protects women, but the limited epidemiological evidence is inconsistent. A substantial body of literature suggests possible mechanisms by which estrogen might prevent atherosclerosis, but less research has been done on the potentially harmful effects of estrogen on coagulation factors and inflammatory processes, or on the contributing effects of male sex hormones. Risk of developing asthma appears to be higher in women who use hormone replacement therapy than in women who do not, but little research has been done on the acute effects of estrogen on airflow, or on potential mediators by which estrogen might increase the risk of asthma. Some diseases (e.g., primary pulmonary hypertension and the rare disease lymphangioleiomyomatosis, known as LAM) occur almost exclusively in women, suggesting that hormones play a role. Research to determine the mechanisms by which diseases develop differently in women than in men will lead to more effective health care interventions for all patients.

Action:

Potential FY 2001 initiative:

- **Increase understanding about the role that sex steroid hormones play in the development of cardiovascular disease.** Investigators will be encouraged to study the effects of sex hormones on cardiovascular disease in existing observational cohorts, using stored blood samples. They will also study how sex hormones, whether produced naturally by the body or administered therapeutically, affect established risk factors, vascular biology, and cardiac function. Gene–hormone interactions will also be examined.

Goal 3. Improve the efficacy of diagnostic testing and treatment approaches in specific population groups.

Evaluating chest pain and diagnosing cardiovascular disease are often more difficult in black patients than in white patients. Diagnostic tests, validated to a far greater extent in whites than in blacks, may not be as useful for black patients as for white patients. One reason, research indicates, is the possibility that racial differences exist in the causes and manifestations of coronary syndromes. For example, the prevalence of heart failure as a sequela of coronary heart disease is higher in blacks than in whites and may be due to physiological differences in the functioning of specific body systems. Therapies focused primarily on relieving chest pain and restoring blood flow to tissues cut off from sufficient blood supplies have been refined in white populations. It is possible that other treatment regimens may be more efficacious in

minority populations because of their higher prevalence of hypertension and diabetes. Evaluation of available diagnostic testing and treatment approaches is needed in individual minority populations.

Action:

Potential FY 2001 initiative:

- **Determine the utility of diagnostic testing for coronary heart disease (CHD) in black populations.** Standard and new diagnostic tests and testing algorithms will be evaluated by comparing their sensitivity, specificity, and predictive value for black and white populations. Relative effectiveness in diagnosing acute and chronic CHD will also be assessed.

Additional action:

- Support clinical trials to compare the relative effectiveness of alternative treatment and reperfusion approaches in black and white patients.

Goal 4. Understand key processes by which environmental, developmental, and psychosocial factors early in life contribute to health disparities later in life.

Despite an overall decline in mortality, disparities in health among different races/ethnicities and socioeconomic groups are increasing. Differences in behavioral risk factors, health knowledge, and access to health care explain only a portion of the disparity. Several theories have been proposed to explain the remaining disparity (e.g., early exposure to adverse environments, development of attitudes and beliefs, and accumulated exposure to psychological stress). These theories need to be investigated in a rigorous manner.

Action:

Potential FY 2001 initiative:

- **Conduct a longitudinal study to evaluate the development of, and exposure to, psychosocial influences that may lead to disparities in health between social strata and among race and ethnic groups.** A random sample of about 15,000 newborn individuals, with a cross-sectional sample of their parents and oversampling for various minority populations, is planned. The study will evaluate, beginning at infancy, psychosocial influences such as psychological stressors, occupational variables, educational resources, and other environmental influences. Psychosocial factors that foster the development of resilience to negative influences on health and the formation of beneficial health habits and practices will also be assessed.

Additional action:

- Identify previously conducted studies of newborns and/or children that contain appropriate biological, psychosocial, socioeconomic, and identifying characteristics, and follow the cohorts for interim morbidity and mortality.

Research Workforce and Research Resources

Goal 1. Use existing study populations more effectively and identify potential new study populations.

Numerous study populations have been established, examined, and followed in NHLBI-supported observational studies and clinical trials. Such study populations are a potential resource for addressing research questions not envisioned when the study was initiated or not emphasized by the original investigators. Research questions related to disease risk usually require long-term follow-up in defined populations; research results would be available much sooner if the required measures were already available or could be performed using stored specimens of study populations from studies continuing under follow-up. Such an approach would be enabled by improved sharing of information, distribution of public use data sets, "user support" for available resources, and support of new research collaborations; it would be cost-effective and it would increase the usefulness of established study populations. In addition, the potential for new study populations, such as the clinical populations defined by longstanding Health Maintenance Organizations, will be assessed.

Action:

- Develop a web site for disseminating information on population-based studies to investigators.

- Publicize availability of information from population-based studies and clinical trials.

- Establish rapid review of collaborative studies proposing to use clinical trial populations.

Goal 2. Increase the use of imaging techniques and improve access to imaging facilities. (see related potential FY2001 initiative: first initiative under Diagnosis of Disease, Goal 1)

Developing resources for minimally invasive imaging is vital for the early detection of cardiovascular, lung and blood diseases. Areas of focus include imaging biosamples at the molecular level; identifying gene products; detecting new markers of diseases at the protein, cell, and extracellular matrix levels; attaching tiny sensors to medical implants (e.g., heart valves, stents) to allow imaging and monitoring of the function of the implants; and targeting cells to allow site-specific delivery of image-contrasting agents or therapeutic drugs. Training scientists in the use of imaging technology and interpreting imaging data, as well as improving access to imaging facilities, are fundamental to this goal.

Action:

- Support research on imaging technology as applied to cardiovascular, lung, and blood diseases and sleep disorders, taking advantage of existing clinical research groups.

- Support training in imaging technology.

- Improve access to imaging facilities.

Goal 3. Support efforts to attract individuals into biomedical science (especially, clinical investigation) and demonstrate career opportunities.

Training young investigators is essential if the United States is to maintain its leadership role in biomedical research. The NHLBI has appointed a diverse group of experts to discuss optimal strategies to deal with current and future research training and career development needs. A workshop on training and career development held in November 1999 provided explicit recommendations to the Institute. Some of the general considerations addressed include: multidisciplinary and interdisciplinary team approaches, ways of dealing with complex diseases, approaches for encouraging diversity in the workforce, expectations in terms of both academic and industrial employment, the nature of mentorship, and clinical research.

Action:

Potential FY 2001 initiative:

- **Augment and strengthen the research capabilities of faculty, students, and fellows at minority medical schools by supporting the enhancement of ongoing (and the development of new) basic, clinical, and population-based research projects.** The proportion of biomedical investigators who are members of underrepresented minority groups is strikingly lower than the percentage of minority U.S. citizens. In the long term, this program will increase the number of minority individuals involved in biomedical research.

Additional action:

- Consider implementation of recommendations of the Expert Panel (described above).

- Organize a cross-disciplinary assessment of issues related to the training of biomedical researchers that addresses such fields as life sciences, bioengineering, computer sciences, physics, and chemistry.

- Begin tracking individuals exposed to research opportunities at the NIH (e.g., in summer programs, intramural fellowships, intramural clinical research programs) and in NIH-supported research programs at all levels of educational institutions throughout the United States.

- Develop a program for supporting young investigators who have finished their training but who are not sufficiently prepared to compete for a traditional NIH research grant.

- Increase flexibility of NIH-supported training programs at institutions throughout the United States and allow individuals to train at multiple sites to increase cross-disciplinary research experiences.

- Improve access to information about NHLBI training programs (e.g., develop interactive web-based approaches).

- Expand collaboration with the private sector in support of training programs.

Goal 4. Develop and test nanoscale systems for understanding cardiovascular, lung, and blood-related biological processes.

The world of nanoscience comprises structures, both natural and synthetic, that are vanishingly small (1 to 100 nanometers, each nanometer being one-billionth of a meter). Nanoscale materials have been shown to exhibit extraordinary properties. For example, scientists have recently discovered a new class of carbon materials, the carbon nanotube, that is a hundred times stronger than, but a fraction of the weight of, a piece of steel of comparable size. Nanotubes could, theoretically, form the structural basis for ultra-small, intracellular imaging systems. Nanoscience and technology might be integrated with disciplines such as imaging and genomic theory to improve diagnostic, preventive, and treatment strategies for cardiovascular, lung, and blood diseases.

Action:

Potential FY 2001 initiative:

- **Support research to adapt theoretical nanoscience for use in developing practical systems.** The program will have two components. First, it will establish the scientific underpinnings necessary to develop nanotechnology that can be used to understand and modify biological processes involved in cardiovascular, lung, and blood disorders. Second, it will test the feasibility of using nanoscience in the design of diagnostic and therapeutic systems, including drug and gene delivery systems.

Goal 5. Develop information resources, and the capability to use them, to enhance research efforts in cardiovascular, lung, and blood diseases and sleep disorders.

Large amounts of research data are currently available, and the volume is rapidly expanding. The usefulness of this information will be improved by increased availability of appropriate bioinformatics tools (i.e., tools for the collection and manipulation of biological data), investigators who are well trained in the use of information systems, and practical ways for collaborating investigators to share their data.

Action:

- Hold a workshop to identify and evaluate bioinformatics needs for cardiovascular, lung, and blood diseases and sleep disorders.
- Identify the many scientific questions that can be addressed by use of existing data sets (without the effort of developing new data), and determine the scientific value of proposed analyses using these existing ("linked") information resources.

- Construct useable information systems.

- Provide training to researchers in the use of information systems.

- Develop funding incentives for bioinformatics research, and encourage the inclusion of bioinformatics research with other research.

- Develop an informatics infrastructure for clinical and basic research, with continued support for updates, maintenance, and user support of established resources.

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